



LMNA gene

lamin A/C

Normal Function

The *LMNA* gene provides instructions for making several slightly different proteins called lamins. The two major proteins produced from this gene, lamin A and lamin C, are made in most of the body's cells. These proteins are made up of a nearly identical sequence of protein building blocks (amino acids). The small difference in the sequence makes lamin A longer than lamin C.

Lamins A and C are structural proteins called intermediate filament proteins. Intermediate filaments provide stability and strength to cells. Lamins A and C are scaffolding (supporting) components of the nuclear envelope, which is a structure that surrounds the nucleus in cells. Specifically, these proteins are located in the nuclear lamina, a mesh-like layer of intermediate filaments and other proteins that is attached to the inner membrane of the nuclear envelope. The nuclear envelope regulates the movement of molecules into and out of the nucleus, and researchers believe it may play a role in regulating the activity (expression) of certain genes.

The lamin A protein must be processed within the cell before becoming part of the lamina. Its initial form, called prelamin A, undergoes a complex series of steps that are necessary for the protein to be inserted into the lamina. Lamin C does not have to undergo this processing before becoming part of the lamina.

Health Conditions Related to Genetic Changes

Charcot-Marie-Tooth disease

At least one *LMNA* gene mutation has been identified in people with a form of Charcot-Marie-Tooth disease known as type 2B1. Charcot-Marie-Tooth disease is characterized by nerve damage, which can result in loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands. The mutation changes a single amino acid in the lamin A and lamin C proteins. Specifically, the amino acid arginine is replaced by the amino acid cysteine at protein position 298 (written as Arg298Cys or R298C). Although its effect is not fully understood, the Arg298Cys mutation alters a region of the protein that is important for interactions with other molecules. It is unclear how the altered proteins contribute to the signs and symptoms of type 2B1 Charcot-Marie-Tooth disease.

Emery-Dreifuss muscular dystrophy

More than 100 mutations in the *LMNA* gene have been identified in people with Emery-Dreifuss muscular dystrophy, a condition characterized by weakness of the muscles used for movement (skeletal muscles) and of the heart (cardiac) muscle. Most of these mutations change single amino acids in lamins A and C, which alters the structure of these proteins. The effect of *LMNA* gene mutations within cells remains unclear. Abnormal versions of lamins A and C may alter the activity of certain genes or weaken the structure of the nucleus, making cells more fragile. Researchers continue to investigate how *LMNA* mutations affect skeletal muscles and cardiac muscle, leading to the characteristic features of Emery-Dreifuss muscular dystrophy.

familial dilated cardiomyopathy

familial partial lipodystrophy

Several mutations in the *LMNA* gene have been found to cause familial partial lipodystrophy type 2, a rare condition characterized by an abnormal distribution of fatty (adipose) tissue in the body. Adipose tissue is lost from the arms, legs, and hips, and excess fat is deposited in the face, neck, and abdomen. The abnormal fat storage is related to changes in the development and function of adipocytes, which are the fat-storing cells in adipose tissue. The effects of *LMNA* gene mutations on adipocytes are not well understood. Studies suggest that these mutations may weaken the nuclear envelope, ultimately leading to the premature death of these cells and leaving the body unable to store and use fats properly. These abnormalities of adipose tissue alter hormone production and affect many of the body's organs. However, it is unclear why the changes cause fat to be lost in some parts of the body and stored abnormally in others.

Hutchinson-Gilford progeria syndrome

A specific mutation in the *LMNA* gene has been found in most patients with Hutchinson-Gilford progeria syndrome, which is a condition that causes the dramatic, rapid appearance of aging beginning in childhood. This mutation changes a single DNA building block (nucleotide) in the gene. Specifically, the mutation replaces the nucleotide cytosine with the nucleotide thymine at position 1824 (written as C1824T). This mutation is also sometimes noted as Gly608Gly or G608G, which refers to the position in the lamin A protein affected by the mutation. Although the C1824T mutation is not predicted to change an amino acid, it alters the way the gene's instructions are used to make a protein. The C1824T mutation leads to an abnormal version of the lamin A protein called progerin, which is missing 50 amino acids near one end. The location of this mutation does not affect the production of lamin C. Other mutations in the *LMNA* gene have been identified in a small number of people with the features of Hutchinson-Gilford progeria syndrome.

The mutations responsible for this disorder result in an abnormal version of lamin A that cannot be processed correctly within the cell. When the altered protein is incorporated into the lamina, it disrupts the shape of the nuclear envelope. Over time, a buildup of this altered protein appears to damage the structure and function of the nucleus, making cells more likely to die prematurely. Researchers are working to determine how these changes lead to the signs and symptoms of Hutchinson-Gilford progeria syndrome.

limb-girdle muscular dystrophy

At least 40 mutations in the *LMNA* gene have been identified in people with limb-girdle muscular dystrophy type 1B. Limb-girdle muscular dystrophy is a group of related disorders characterized by muscle weakness and wasting, particularly in the shoulders, hips, and limbs.

LMNA gene mutations that cause limb-girdle muscular dystrophy may impair the function of lamin proteins. Impaired lamin protein function may lead to a fragile, easily-damaged cell nucleus or improperly regulated genes that affect a variety of cell activities. It is not known how the effects of *LMNA* gene mutations relate to the specific signs and symptoms of limb-girdle muscular dystrophy.

mandibuloacral dysplasia

At least four mutations in the *LMNA* gene cause mandibuloacral dysplasia type A (MADA). This condition is characterized by a variety of signs and symptoms, which can include bone abnormalities; mottled or patchy skin coloring; and loss of fatty tissue under the skin, particularly affecting the limbs (type A lipodystrophy). The *LMNA* gene mutations that cause this condition change single amino acids in the lamin A and lamin C proteins. The most common mutation replaces the amino acid arginine at position 527 with the amino acid histidine (written as Arg527His or R527H).

The effects of *LMNA* gene mutations in this condition are not well understood. The amino acid changes may affect the structure of the lamin A or lamin C protein, or both, and alter how they interact with other proteins in the nuclear lamina. Some researchers speculate that these changes disrupt the nuclear envelope, making cells more fragile; however, it is unclear how the altered lamin proteins contribute to the signs and symptoms of MADA.

other disorders

Mutations in the *LMNA* gene have been found to cause several other inherited conditions. Because the conditions result from mutations that affect lamin proteins, they are known as laminopathies.

Familial dilated cardiomyopathy with conduction defects has severe effects on cardiac muscle that result in life-threatening heart problems. The features of this

disorder, and also those of limb-girdle muscular dystrophy type 1B, overlap with those of the autosomal dominant form of Emery-Dreifuss muscular dystrophy (described above). Because certain *LMNA* mutations may be responsible for any of these conditions, researchers suspect that limb-girdle muscular dystrophy type 1B and familial dilated cardiomyopathy with conduction defects may be variants of Emery-Dreifuss muscular dystrophy instead of separate disorders.

Mutations in the *LMNA* gene also cause atypical progeroid syndrome (APS); the features of this condition are similar to those of Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia (described above). As in Hutchinson-Gilford progeria syndrome, children with APS look as though they are aging prematurely, although the signs and symptoms of APS usually begin slightly later in life. APS can also cause similar abnormalities in bone development and fat distribution as mandibuloacral dysplasia, although they are typically milder in APS.

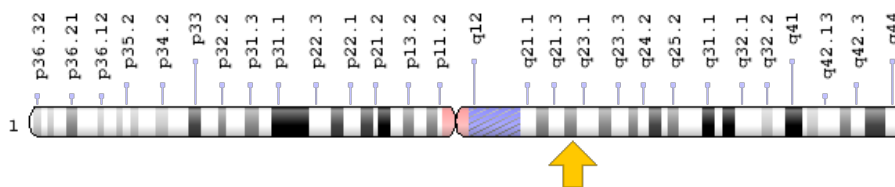
Mutations in the *LMNA* gene have been identified in newborns with a disorder called lethal restrictive dermopathy. Infants with this disorder have tight, rigid skin; underdeveloped lungs; and other abnormalities. They do not usually survive past the first week of life.

Researchers have not determined how mutations in the *LMNA* gene result in this diverse group of disorders, but the multiple roles of the nuclear lamina in cells may help explain the wide variety of signs and symptoms.

Chromosomal Location

Cytogenetic Location: 1q22, which is the long (q) arm of chromosome 1 at position 22

Molecular Location: base pairs 156,082,546 to 156,140,089 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- LMN1
- LMNA_HUMAN

Additional Information & Resources

Educational Resources

- Madame Curie Bioscience Database: Laminopathies: One Gene, Two Proteins, Five Diseases.
<https://www.ncbi.nlm.nih.gov/books/NBK6151/>
- University of Washington Neuromuscular Disease Center
<http://neuromuscular.wustl.edu/musdist/lg.html#1b>

GeneReviews

- Charcot-Marie-Tooth Neuropathy Type 2
<https://www.ncbi.nlm.nih.gov/books/NBK1285>
- Congenital Muscular Dystrophy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1291>
- Dilated Cardiomyopathy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1309>
- Emery-Dreifuss Muscular Dystrophy
<https://www.ncbi.nlm.nih.gov/books/NBK1436>
- Hutchinson-Gilford Progeria Syndrome
<https://www.ncbi.nlm.nih.gov/books/NBK1121>
- Limb-Girdle Muscular Dystrophy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1408>
- LMNA-Related Dilated Cardiomyopathy
<https://www.ncbi.nlm.nih.gov/books/NBK1674>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28LMNA%5BTIAB%5D%29+OR+%28lamin+A/C%5BTIAB%5D%29+OR+%28lamin+A%5BTI%5D%29+OR+%28lamin+C%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- CARDIOMYOPATHY, DILATED, 1A
<http://omim.org/entry/115200>
- LAMIN A/C
<http://omim.org/entry/150330>
- RESTRICTIVE DERMOPATHY, LETHAL
<http://omim.org/entry/275210>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_LMNA.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=LMNA%5Bgene%5D>
- HGNC Gene Family: Lamins
<http://www.genenames.org/cgi-bin/genefamilies/set/612>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=6636
- Inherited Peripheral Neuropathies Mutation Database
<http://www.molgen.ua.ac.be/CMTMutations/Mutations/Mutations.cfm?Context=21>
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/4000>
- UniProt
<http://www.uniprot.org/uniprot/P02545>

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